Respectfully submitted,

Christine A. Goddard, Ph.D.
Registration No. 46,731

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WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The section on page 1 having the section heading **CROSS REFERENCE TO RELATED APPLICATIONS** has been amended as follows.

This application is a continuation of U.S. Ser. No. 09/349,007, filed July 7, 1999, which in turn is a continuation-in-part of U.S. Ser. No. 09/115,025, filed July 14, 1998, the disclosures of each of which are incorporated herein by reference in their entireties [the content of which is incorporated herein by reference in its entirety].

Table I on page 50 has been amended as follows.

Table I
Oligonucleotides containing Staggered PS/PO linkages

Oligo #	ISIS #	Sequence (5'-3')[1]	Backbone	Chemistry	Target
1	18268 staggered oligomer	5'-T_S**C^m_O** T_S**G_O** A_S**G_O** T_S**A_O** G_S**C^m_O** **$A_S$$G_O$** A_S**G_O** G_S**A_O** G_S**C^m_O** T_S**C**-3' SEQ ID NO: 1	P=S/P=O	2'-*O*-MOE	*Human ICAM-1*
2	22592 staggered gapmer	5'-**$A_S$$T_0$$G_S$$C^m_0$$A_S$$T_0$** $T_S$$C_S^{m}T_S$$G_S$ $C_S^{m}C_S^{m}C_S^{m}C^m$**O** **$C^m_S$$A_0$$A_S$$G_0$$G_S$A**-3' SEQ ID NO: 2	P=S/P=O	2'-*O*-MOE & 2'-H	*mouse C-raf*
3	25303 staggered hemimer	5'-$G_S$$C^m_S$$C^m_S$$C^m_S$$A_S$$A_S$$G_S$$C^m_S$$T_S$$G_S$$G_S$$C^m$**O** **$A_S$$T_O$$C^m_S$$C^m_O$$G_S$$T_O$$C^m_S$A**-3' SEQ ID NO: 3	P=S/P=O	2'-*O*-MOE & 2'-H	*Human ICAM-1*

[1] All nucleosides in bold are 2'-*O* -MOE (2'-O-CH_2-CH_2-O-CH_3)

Table III on page 51 has been amended as follows.

Table III
Tm Values of Human ICAM-1 Antisense Oligonucleotide ISIS 3067 and Analogs Against RNA Target

5'-TCT GAG TAG CAG AGG AGC TC-3' (SEQ ID NO:4)		
Oligonucleotide	**Modifications**	**Tm**
ISIS 3067 (SEQ ID NO: 5)	**P=S, 2'-deoxy DNA**	**50.1**
ISIS 11910 (SEQ ID NO: 4)	**P=O, 2'-deoxy DNA**	**58.4**
ISIS 11159 (SEQ ID NO: 6)	**P=S, 2'-MOE**	**79.2**
ISIS 11158 (SEQ ID NO: 7)	**P=O, 2'-MOE**	**86.6**
ISIS 18268 (SEQ ID NO: 8)	**P=O/P=S, STAGGERED 2'-MOE**	**84.0**

Table IV on page 53 has been amended as follows.

Table IV
Controlling P=S Linkages: ICAM-1 Activity with Alternating P=S/P=O Linkages in a Uniform 2'-modified Oligomer

Isis #	Oligonucleotides Tested	
16952 (SEQ ID NO: 9)	**TCTGAGTAGCAGAGGAGCTC**	MOE, P=O
16953 (SEQ ID NO: 10)	GATCGCGTCGGACTATGAAG	**Scrambled Control[a]**
15537 (SEQ ID NO: 11)	TCTGAGTAGCAGAGGAGCTC	**MOE, P=S**
16954 (SEQ ID NO: 12)	GATCGCGTCGGACTATGAAG	**Scrambled Control**
18268 (SEQ ID NO: 13)	TCTGAGTAGCAGAGGAGCTC*	**MOE, P=S/P=O**

C=5-methyl -C in all sequences (except C*)

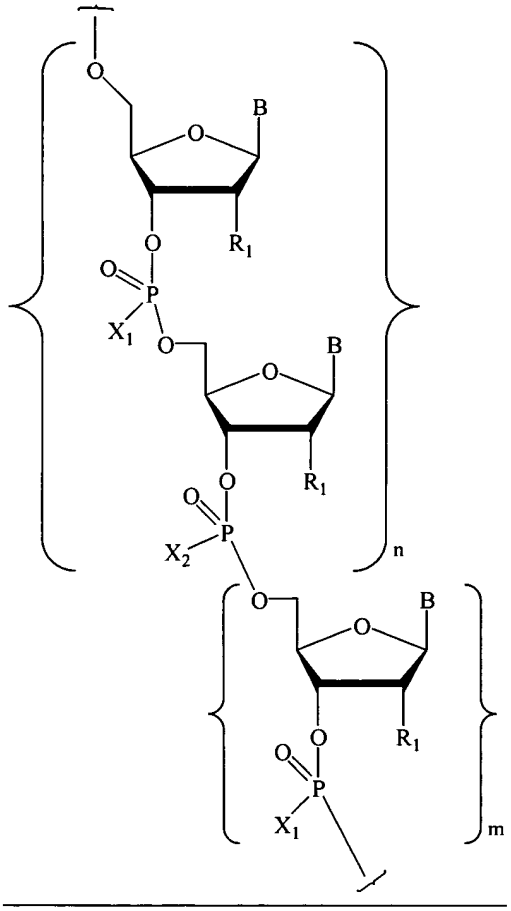
[a]same base composition

In the claims:

Claims 34-51 have been added.

Claims 28-30 have been rewritten as follows.

28. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of [claim 1.] formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_v$;

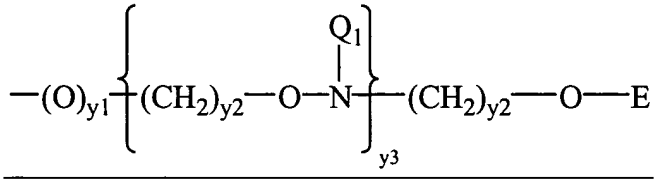
Z is O, S, NH, or N-R_{22}-$(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



wherein:

y1 is 0 or 1;

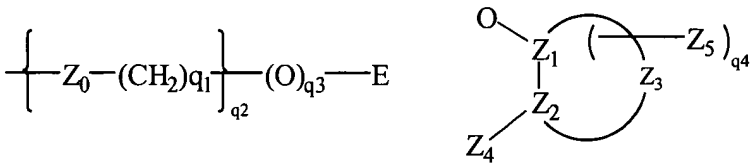
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



I II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

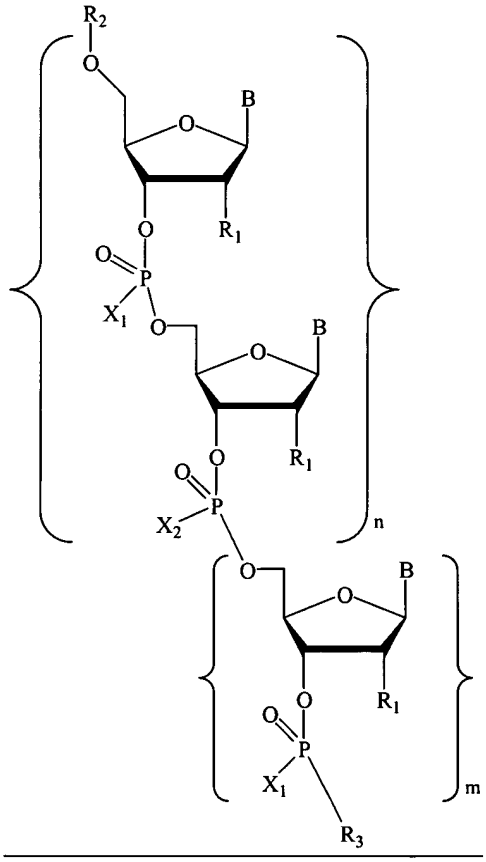
Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1.

29. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of [claim 7.] formula:



wherein:

each B is a nucleobase;

X_1 is S;

X_2 is O;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_v$;

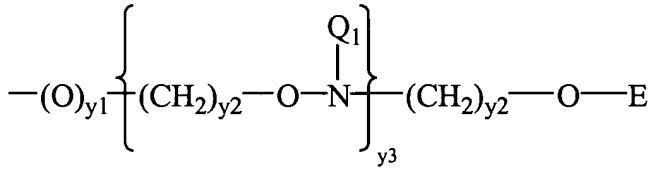
Z is O, S, NH, or N-R_{22}-$(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

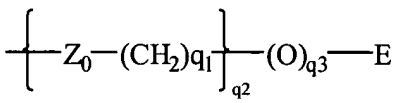
y2 is independently 0 to 10;

y3 is 1 to 10;

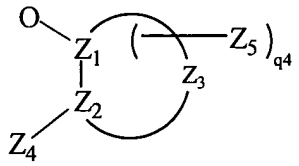
E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



I



II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide; and

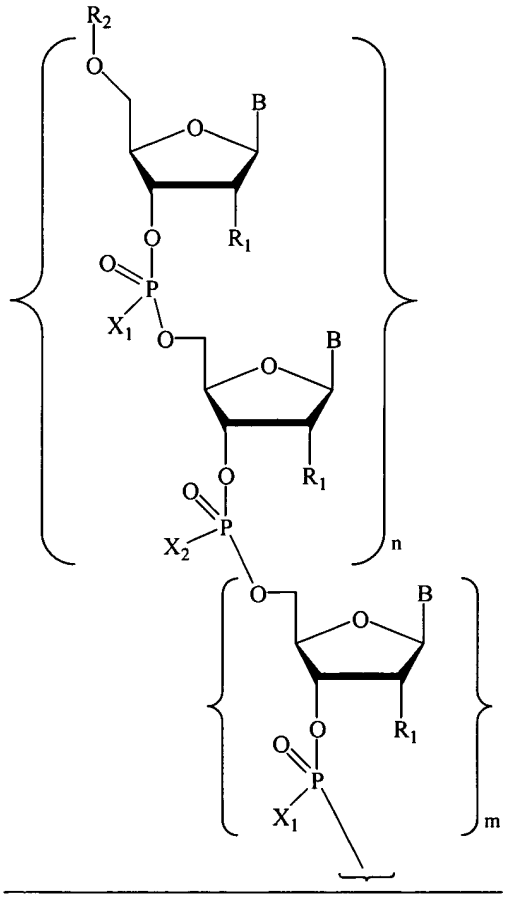
R_3 is OH, an oligonucleotide, or a linker connected to a solid support.

30. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of [claim 13.] formula:

$$(5')\ W^1\text{-}W^2\text{-}W^3\ (3')$$

wherein:

W^1 has the Formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_v$;

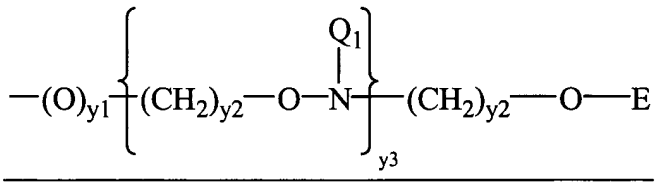
Z is O, S, NH, or N-R_{22}-(R_{23})$_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, poly-alkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

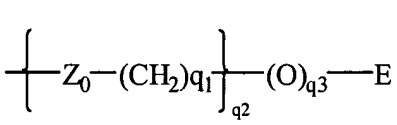
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C_1-C_{10} alkyl, N(Q_1)(Q_2) or N=C(Q_1)(Q_2);

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



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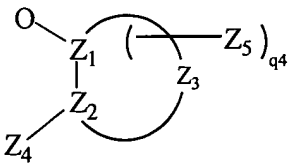


II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

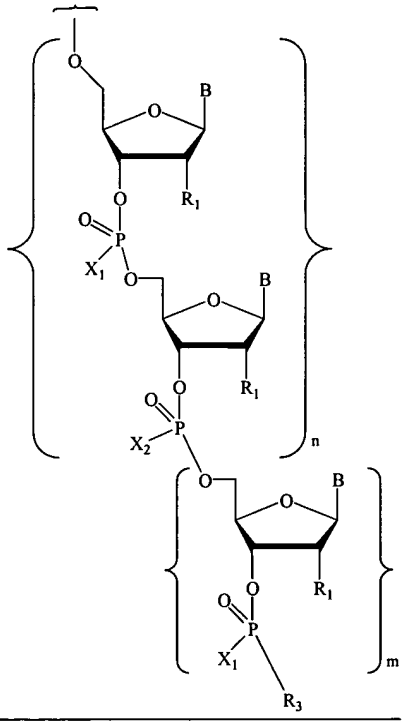
Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide;

W^3 has the Formula:



wherein R_3 is OH, an oligonucleotide, or a linker connected to a solid support; and

W^2 is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.